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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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08/872,527 06/11/97 GUD

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022249  
LYON & LYON LLP  
SUITE 4700  
633 WEST FIFTH STREET  
LOS ANGELES CA 90071-2066

HM12/0120

EXAMINER

DIBRINO, M

ART UNIT

PAPER NUMBER

1644

DATE MAILED:

01/20/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

# Office Action Summary

Application No.  
**08/872,527**

Applicant(s)

Guo

Examiner  
**Marianne DiBrino**

Group Art Unit  
**1644**



☒ Responsive to communication(s) filed on Oct 19, 1999

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1035 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

## Disposition of Claim

☒ Claim(s) 1-22 and 33-65 is/are pending in the application

Of the above, claim(s) 5, 11, 14-19, 39-48, 55, 56, 58-62, 64, and 65 is/are withdrawn from consideration

☐ Claim(s) \_\_\_\_\_ is/are allowed.

☒ Claim(s) 1-4, 6-10, 12, 13, 20-22, 33-38, 49-54, 57, and 63 is/are rejected.

☐ Claim(s) \_\_\_\_\_ is/are objected to.

☐ Claims \_\_\_\_\_ are subject to restriction or election requirement.

## Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on \_\_\_\_\_ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some\* ☒ None of the CERTIFIED copies of the priority documents have been  
☐ received.

☐ received in Application No. (Series Code/Serial Number) \_\_\_\_\_

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\*Certified copies not received: \_\_\_\_\_

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

## Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s) \_\_\_\_\_

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

### DETAILED ACTION

1. The Art Unit location and the examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1644.

2. Applicant's amendment, filed 10-19-99 (Paper No. 15), is acknowledged and has been entered.

a. With regard to Applicant's comments in section IV, that claims 5, 11, 14-15, 16-17, 18-19, 39-41, 42-48, 55-56, 58-62 and 64-65 are not different species and should be examined with claims 1-4, 6-10, 12, 13, 20-22, 33-38, 49-54 and 63, Applicant's argument has been considered and is not deemed persuasive for the following reasons.

The elected species is a bispecific bridge molecule, i.e., an antibody which binds to gp55 and to CD28. The claims in dispute are drawn to patentably distinct species. For example, the species of claims 16, 17, and 55 (method or composition claims) is two different bridge molecules, the species of claims 18, 19, 48, 56, 42-44, and 45 (method or composition claims) is a trispecific bridge molecule, the species of claims 46 and 47 (method claims) is two different bridge molecules which are trispecific. For instance, claims 5, 58-61, 64 and 65 are different methods involving further administration of cytokines (claims 39, 41) or different methods involving different T cell adhesion molecules, MHC genes, cytokine genes or primary or secondary costimulatory molecule genes transferred into the target disease cell. For example, the compositions of claims 14 and 15 are distinct because they are virally infected target diseased cells, which may have different antigen expression profiles from non-virally infected target diseased cells.

b. Claims 1-4, 6-10, 12, 13, 20-22, 33-38, 49-54 and 63 are being acted upon presently.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 33-38, 49-51, 57 and 63 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not disclose how to use the instant invention for the curing of patient mammals of diseased cells. The claimed methods encompass methods of curing a human patient suffering from cancer. The specification has not enabled the

breadth of the claimed invention in view of the teachings of the specification because the claims encompass methods for curing cancer in vivo in humans. The state of the art is such that it is unpredictable in the absence of appropriate evidence whether the claimed compositions can be used for curing cancer in vivo in humans. The specification discloses no working examples with regards to the use of the instant invention for the curing of disease in vivo in humans.

The instant application discloses (on pages 37-39 and 40-42) use of the invention to cause hepatoma tumor cell regression in mice and to cause tumor regression of EL-4 lymphoma and SMCC-1 colon carcinoma in mice, respectively.

It has been art-recognized experience that for any novel therapy, the transition from the laboratory to the clinic (animal experiments to the bedside) is a quantum leap (Chatterjee et al., Cancer Immunol. Immunother., 1994; see Introduction). Results obtained under controlled conditions and in inbred animals often differ from the clinical response obtained in patients. This applies in particular to strategies based on immune responses, including strategies drawn to cancer therapy. Concerning animal models, the response of animals to chemotherapy, radiation and surgery is generally predictive of their effect in human patients (Osband et al., Immunol. Today 11: 193-195, 1990). Tumor burden and antigenic drift continue to present serious burdens for successful cancer therapy in vivo. Tumors are classified as immunogenic or non-immunogenic, solid or hematological in nature. Effective cancer strategies should be designed to deal effectively with the nature of each of these classifications.

For these reasons, it is not clear that reliance on the invention to cause tumor regression in mice of three tumor cell types accurately reflects the relative efficacy of the claimed therapeutic strategy in curing cancer in humans.

There is insufficient guidance in the specification as to how to practice the method of the instant invention. Undue experimentation would be required of one skilled in the art to practice the instant invention using the teaching of the specification alone. See Ex parte Forman, 230 USPQ 546, BPAI, 1986.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103<sup>©</sup> and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

§ 3

7. Claims 1-4, 6, 8-10, 12, 13, 20-22 and 52<sub>^</sub> are rejected under 35 U.S.C. 102(a) as being anticipated by Shi et al (Proc. Amer. Assoc. Cancer Res. March 1996, Volume 37, page 480, Abstract No. 3278).

Shi et al teach a composition comprising human liver tumor cells which are treated in vitro with cytokines IFN- $\gamma$  and TNF and mixed with bispecific monoclonal antibody to CD28, a costimulatory molecule on T cells, and the tumor-specific antigen GP115X. Shi et al teach said composition is used to generate tumor-specific CTL in vitro. Shi et al teach said human liver tumor cells with increased expression of Class I MHC molecules, ICAM-1 and B7. Claim 7 is included because the reference is silent as to the subtype of TNF is used. Claims 21, 22 and 53 are included because the reference is silent as to what buffer the cells are in. The composition taught by Shi et al is present in tissue culture media (e.g., a pharmaceutically acceptable carrier).

The reference teachings anticipate the claimed invention.

8. Claim 7 is rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Shi et al (Proc. Amer. Assoc. Cancer Res. March 1996, Volume 37, page 480, Abstract No. 3278) as evidenced by Rink (Int. Arch. Allergy Immunol. 1996, Vol. 111, pages 199-209).

Shi et al teach a composition comprising human liver tumor cells which are treated in vitro with cytokines IFN- $\gamma$  and TNF and mixed with bispecific monoclonal antibody to CD28, a costimulatory molecule on T cells, and the tumor-specific

antigen GP115X. Shi et al teach said composition is used to generate tumor-specific CTL in vitro. Shi et al teach said human liver tumor cells with increased expression of Class I MHC molecules, ICAM-1 and B7.

While Shi et al do not disclose the subtype of TNF used, they disclose that increased expression of several primary/costimulatory molecules using TNF and IFN-g. Rink et al teach that "TNF" is used synonymously with "TNF-a" (especially Abstract, first line).

Therefore the claimed composition appears to be the same or similar to that of the prior art absent a showing of unobvious differences, as does the pharmaceutically acceptable carrier. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on applicant to show an unobvious distinction between the composition of the instant invention and that of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

9. Claims 1-4, 6-10, 12, 13, 20-22, 33-38, 49-54 and 63 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Wang et al (*Int. J. Cancer*, Vol. 51, pages 962-967, 1992) or Vanky et al (*Semin. Cancer Biol.*, Vol. 2(1), pages 55-62, 1991) in view of Renner et al (*Science*, Vol. 264, page 833, 1994) or Bohlen (*Blood*, vol. 82, pages 1803-1812, 1993), admissions in the specification, Darlington et al (*JNCL*, Vol. 64, page 809, 1980), Chapoval et al (*J. Immunol.*, Vol. 155, pages 1296-1303, 1995) and Krummel et al (*J Exp. Med.*, Vol. 182, pages 459-465, 1995).

Applicant's argument has been considered, but is not deemed persuasive for the reasons of record in Paper No. 14, mailed 7/14/99 and for the reasons stated below.

Concerning Applicant's comments on the Wang et al reference, Wang et al teach cytokine-induced elevation of MHC class I molecules in tumor cells (especially second full paragraph on page 962, and the Materials and Methods section). These tumor cells then were then subsequently used to initiate MLTC. With regard to Applicant's Declaration under 37 C.F.R. 1.132, in particular items 7-9 and 5, Applicant has not repeated the method of Wang et al with Applicant's tumor cell lines because as stated above, Wang et al did not treat mixtures of tumor cells and T cells with cytokines as did Applicant. Wang et al does not teach a vaccine comprising functional T cells, tumor cells and bispecific antibodies, therefore, Applicant's argument in item 5 is moot. Furthermore, Chapoval et al teach in vivo use of bispecific antibody and the antitumor efficacy of this approach (especially Abstract). Also, in response to applicant's arguments against the references

individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *in re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

With further regard to Applicant's Declaration under 37 C.F.R. 1.132, in particular item 4, Applicant's argument has been considered, but is not deemed persuasive because the issue at hand is likely to be concentration dependence. Applicant is reminded that declarations must set forth facts, not merely conclusions. In *re Pike et al.*, 84 USPQ 235. In addition, Figure 6 in Applicant's Declaration appears to show results of experiments in which T cells are also administered (e.g., complex and T cells) and this is not the claimed invention. Furthermore, the instant claims are not restricted to "non or weakly immunogenic tumors". The scope of the purported unexpected results is not commensurate with the scope of the claimed invention. And again in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *in re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

With regard to Applicant's comments in item 6 of Applicant's Declaration under 37 C.F.R. 1.132, the combined art drawn to the species anticipates the genus.

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 1-4, 6-10, 12, 13, 20-22, 33-38, 49-54, 57 and 63 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6, 10, 11, 7-9, of copending Application No. 09/216,604. Although the conflicting claims are not identical, they are not patentably distinct from each other because it would have been obvious to remove unbound bridge molecule (claim 6 in '604), it would be obvious to use the costimulatory molecules listed in instant claim 4, it would have been obvious to treat target diseased cells with the cytokines listed in instant claim 8 which are known in the art for the purpose stated, it would have been obvious to use the binding sites or antigens listed in the instant claims which were known in the art, a pharmaceutical composition used for treating a human patient would first be tested in an animal, it would have been obvious to increase costimulatory molecules in vitro with cytokines or in vivo. Therefore, the two sets of claims would have been prima facie obvious to one of ordinary skill in the art.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

12. No claim is allowed.

13. Application serial no. 60/019,639 was not available to the Examiner at this time. It would expedite prosecution if Applicant could provide a copy of said application.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne DiBrino whose telephone number is (703) 308-0061. The examiner can normally be reached Monday through Friday from 8:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

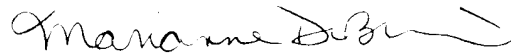
Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must



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conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.



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January 18, 1999



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